Effect of Vitamin E, Vitamin C, and -Carotene on stroke risk

Suter, Paolo M

Abstract: In a recent prospective observational study, vitamins C and E and -carotene did not elicit protective effects on stroke risk. Lutein, however, may elicit such protection. Nevertheless, these nutrients may be important modulators of the outcome after the occurrence of a stroke. At present, optimal control of the classic stroke risk factors in combination with increased consumption of fruits, vegetables, and antioxidant nutrients may represent the safest and most efficient strategy to control stroke risk

DOI: https://doi.org/10.1111/j.1753-4887.2000.tb01859.x

Effect of Vitamin E, Vitamin C, and ß-Carotene on Stroke Risk

In a recent prospective observational study, vitamins C and E and ß-carotene did not elicit protective effects on stroke risk. Lutein, however, may elicit such protection. Nevertheless, these nutrients may be important modulators of the outcome after the occurrence of a stroke. At present, optimal control of the classic stroke risk factors in combination with increased consumption of fruits, vegetables, and antioxidant nutrients may represent the safest and most efficient strategy to control stroke risk.

Stroke mortality is the third leading cause of death in the United States,[1,2] after cardiovascular diseases and cancer. Although the pathogeneses of these three leading causes of death may be very different, they share several risk factors. Present evidence suggests that reactive oxygen species such as superoxide anions or singlet oxygen may play an important role in the pathogenesis of all three, including affecting the outcome of the different forms of stroke.[3–5] For example, vitamin E may reduce the risk of atherosclerotic heart disease through its inhibitory effects on low-density lipoprotein cholesterol oxidation, platelet function, or enthothelial function.[5] Atherosclerotic disease processes are similar in vascular beds other than the coronary arteries, and thus it is plausible that vitamin E alone or in combination with other antioxidant nutrients may play a role in the pathogenesis of stroke.

A recent study by Ascherio et al.[6] examined the effects of vitamin E, vitamin C, and carotenoids (β-carotene and lutein) on ischemic stroke risk in the cohort of the Health Professionals Follow-up Study. In this prospective observational study, more than 43,000 subjects were observed during an 8-year follow-up period. The study participants were all men ages 40 to 75 who did not have cardiovascular disease or diabetes mellitus. Dietary intake was assessed by a self-administered food frequency questionnaire. During the observation period, 328 strokes (210 ischemic, 70 hemorrhagic, and 48 unclassified) occurred. Vitamin E and vitamin C intake (independently, whether from diet or supplements) had no significant effect on overall stroke risk (independent of the type of stroke). The relative risk (RR) for ischemic stroke in the top quintile of vitamin C intake (with a median intake of 1167 mg/day) by comparison with the bottom quintile (median intake of 95 mg/day) was 1.03 (confidence interval [CI], 0.66–1.59, nonsignificant). The analysis of the RR for total stroke in relation to vitamin C intake was similar.

This review was prepared by Paolo M. Suter, M.D., M.S., Medical Policlinic, University Hospital, 8091 Zürich, Switzerland.

The age-adjusted RR for ischemic stroke in the top quintile of vitamin E intake (411 international units [IU]/day) compared with the bottom quintile of vitamin E intake (5.4 IU/day) was 1.18 (95% CI, 0.77–1.82; $P > 0.2$ for trend). The effects of this vitamin on the RR for total stroke were similar.[6] Hemorrhagic stroke risk was slightly higher in the top quintiles of vitamin E intake, although this effect did not reach the level of significance (RR = 1.31; CI, 0.62–2.76).

Interestingly, β-carotene and lutein intakes were inversely related to the risk of ischemic as well as total stroke, although multivariate analysis did attenuate the significance of β-carotene's effect on stroke risk.[6] The intake of lutein was associated with a marginally significant reduction of ischemic stroke risk (RR = 0.63; CI, 0.4–0.99; $P = 0.1$ for trend). The reduction of the effect of carotenoids on stroke risk in this study may be caused by the colinearity of carotenoids with other nutrients.

Some earlier studies reported a protective effect of vitamin C on stroke risk,[7,8] whereas other studies did not find a protective effect of vitamin C.[9–11] The differential effects of vitamin C may be due to other population characteristics, which may be of importance as stroke risk factors and may remain uninfluenced by vitamin C (e.g., genetic background). This is also supported by the results of a prospective study from Shanghai in which no significant association was found between vitamin C and vitamin E intake.[10] Additionally, in the large supplementation trial from Linxian, no effect of vitamin C supplements was seen on stroke risk.[12] Although the two Chinese studies were done in rather different regions, some stroke risk factors may prevail without influence by the nutrients of interest in the present review.

The relationship between vitamin E nutriture and stroke risk seems to be less controversial. A large Finnish trial reported an increased risk of stroke with vitamin E supplementation (RR = 1.5).[13] Even though in the Linxian Trial a similar dose of vitamin E was given, no significant effect on stroke risk was seen.[12] These two studies are, however, very different regarding baseline nutriture as well as other baseline conditions, so they cannot be compared. Nevertheless, it can be concluded that in these older studies vitamin E was not associated with a protective effect on the risk of stroke. Similarly, in the study by Ascherio et al.,[6] the risk for hemorrhagic stroke was slightly higher in the top quintile of vitamin E intake (RR = 1.31; CI, 0.62–2.76). The median vitamin E intake in the top quintile was 411 IU/day compared with 5.4 IU/day in the bottom quintile. This can be explained by the effect of vitamin E on vitamin K metabolism,[14,15] which elicits an anticoagulatory effect and a higher bleeding tendency. Despite these known pharmacologic effects of vitamin E on vitamin K,

the effect on hemorrhagic stroke risk is not surprising, and the lack of significance may be explained by the relatively low mean and median intake of vitamin E in the top quintile of intakes, in which 93% of the subjects were taking supplements. In contrast, in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, even with α-tocopherol supplementation of 50 IU/day a significant increase in hemorrhagic stroke risk was found.[13] These data illustrate nicely that each single nutrient alone or in combination may have favorable as well as unfavorable effects.

Accordingly, the indication for supplementation of certain nutrients should be formulated very carefully. Although there is no conclusive prospective evidence for the role of vitamin E in the prevention of cardiovascular disease, vitamin E supplement doses of 100–400 IU/day are recommended.[5] This amount may be much too high for certain subjects owing to an increase in bleeding tendency, which can be further increased by the ingestion of warfarin and/or acetylsalicylic acid.[16]

Studies regarding the association between carotenoids and stroke risk are rare. Two studies reported an increased risk for stroke upon β-carotene supplementation.[13,17] The data are controversial and no conclusion regarding the effect of β-carotene can be made. There are several hundreds of carotenoids found in nature, and it is conceivable that some of them may have protective effects, whereas others may have deleterious effects. In the present study, lutein seems to have a protective effect on stroke risk. Some of the major sources of lutein are dark-green leafy vegetables.

In an earlier study, Ascherio et al.[18] reported an inverse association between the risk of stroke and the intake of potassium, magnesium, and cereal fiber. This is in agreement with the suggestion that carotenoid and lutein nutriture are indicators of a healthy diet, rich in fruits and vegetables that are the principal sources of potassium, fiber, and vitamin C.[19] The latter observation also supports the concept that the overall diet has a more significant effect on risk reduction than any one single nutrient. This agrees with current recommendations to ingest an overall balanced diet that is rich in fruits and vegetables[20] as well as the "one diet fits all" concept,[21] which promotes such a diet during all periods of life, from the "cradle to the grave."

There are innumerable studies reporting protective effects of a diet rich in vegetables and fruits for most diseases, including cardiovascular disease and cancer.[22–25] In view of the complex mixture of nutrients and protective agents (i.e., phytochemicals) in fruits and vegetables, it is impossible to identify a single "miracle" nutrient for protection from certain diseases. It is most likely the "natural" mix of chemicals that elicits protection, and present evidence suggests that this natural mix of chemicals is more important than any one nutrient that can be added to the diet in the form of a supplement.

The recommendation to obtain the essential nutrients (e.g., the Recommended Daily Allowance) from the diet whenever possible is also reflected in the findings from Ascherio et al.[6] in that neither the dose nor the duration of vitamin E and/or vitamin C supplement intake favorably affected total or ischemic stroke risk. Although certain people require specific recommendations (e.g., children, women, some elderly), the formulation of general recommendations that are understandable, easy to follow, and feasible is important. The concept of a diet that fits all individuals is very attractive and is probably the most promising for disease prevention in the long run.[21] Present evidence suggests that there is no single miracle nutrient for the prevention and/or treatment of chronic diseases; individuals with healthy lifestyles that include a healthful diet, however, stand a greater chance of reaping these benefits.

The results of the present study[6] are in agreement with earlier studies,[8,11] which reported conflicting results regarding the protective effects of these nutrients on stroke risk. As the authors point out,[6] different studies cannot be compared owing to miscellaneous limitations such as the prevalence of malnutrition or various supplement intakes. Accordingly, the intake of certain nutrients represents more of an indicator of risk than specific risk factors. In the study by Ascherio et al.,[6] the significant association between stroke risk and lutein as well as β-carotene is probably a proxy for a high intake of fruits and vegetables.

The potential preventive effects of single nutrients vary from one study to the next owing to factors such as overall diet, lifestyle, age, baseline nutritional status, and study duration (i.e., length of follow-up). This is illustrated by the lack of a relationship between vitamin C intake and stroke risk in the present study.[6] The intake of vitamin C in this population varied widely and tended to be more than the present recommendation, even in the bottom quintile. Another recent study[8] reported a strong negative relationship between biochemical vitamin C status and dietary intake of vitamin C and the risk of stroke during a follow-up period of 20 years in elderly subjects (ages > 65 years). In the study by Ascherio et al.,[6] the participants' age range was 40–75 years, and the duration of follow-up was only 8 years. These factors related to the study design may be important modulators of the outcome, especially in relation to chronic diseases.

The present study[6] is of great public health importance because stroke-related morbidity and mortality are of primary concern to the public. The negative results of this study are not at all disappointing, but rather underline the complexity of the disease entity that is summarized as stroke. Stroke represents a group of different diseases with varying pathophysiologic bases.[2,26] Different modifiable risk factors for stroke have been identified and

the control of these risk factors will reduce the risk of stroke considerably.[2] To conclude from the data of Ascherio et al.[6] that vitamins do not play an important role in reducing stroke risk may be very wrong. When considering disease risk, one must consider the pathogenesis, progression, therapy, and final outcome.

Overall nutrition as well as single nutrients may affect the different stages of the disease process differently. There are several lines of experimental and observational evidence suggesting that an adequate supply of the vitamins discussed in this article may result in an improved outcome after the occurrence of a stroke.[4,9,27–29] Animal studies have reported an outcome in different stroke models that depends upon nutritional factors.[30] Ischemia in general, especially cerebral ischemia, followed by reperfusion (and thus reoxygenation) induces increased free radical production and injury that is not directly related to the initial hypoxia. This phenomenon is called reoxygenation injury, and vitamin E has been shown to reduce such reoxygenation injury after hypoxia, owing to a lowering of free radical damage.[31] Accordingly, the size of the infarct is larger in vitamin E–deficient animals by comparison with animals with better vitamin E nutriture. In stroke patients, lower vitamin E and carotenoid levels, as well as lipid peroxidation markers, have been described. At present, however, it is not known whether such changes in antioxidant status are the cause or the consequence of the cerebrovascular event.

In several studies, a reduction in stroke and overall cardiovascular risk was associated with increased consumption of fruits and vegetables.[18,32–34] Additionally, in intervention studies,[35] a decrease in stroke risk upon supplementation with vitamins and/or trace elements has been reported. One recent supplementation trial in Linxian reported a stroke risk reduction of 55% (RR = 0.45, $P < 0.05$).[35] Another study reported that subjects with low baseline serum selenium levels showed a higher stroke mortality during a follow-up period of 9 years.[36] In agreement with these observations, stroke patients showed lower antioxidant vitamin levels as well as increased biochemical lipid peroxidation parameters within 24 hours of the clinical event.[4] The controversial findings from experimental and epidemiologic studies could be explained by the fact that stroke is a very heterogeneous disease. Furthermore, the occurrence of a clinical event may impose acute overall stress including metabolic stress with an increased requirement for antioxidative nutrients so that short-term alterations of different biochemical parameters (nutrients as well as peroxidation parameters) may occur, although they are not directly related to the pathogenesis.

From the present evidence it can be said that the classical risk factors[2] are of more importance than nutritional factors in the pathogenesis of stroke. Nevertheless, the classical risk factors can be modulated by nutritional factors such that if a stroke occurs, the outcome may be better in a patient with a better overall nutriture.

There is no single cause or risk factor for stroke. Hypertension probably represents the most consistent risk factor, and stroke is mainly caused by insufficient control of this classical risk factor.[2,26] Undertreatment of hypertension has been identified as one of the leading causes of excess stroke mortality and morbidity in hypertensive subjects.[37] In view of the scale of stroke morbidity and mortality, the search for stroke risk factors will and has to go on. At present, optimal control of the classical stroke risk factors combined with increased consumption of fruits, vegetables, and antioxidant nutrients may represent the safest and most efficient strategy to control stroke risk.

1. Warlow CP. Epidemiology of stroke. Lancet 1998; 352(suppl III):1–4
2. Gorelick PB, Sacco RL, Smith DB, et al. Prevention of the first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. JAMA 1999;281: 1112–20
3. Gey KF. Vitamins E plus C and interacting conutrients required for optimal health. Biofactors 1998;7:113–74
4. Chang CY, Lai YC, Cheng TJ, et al. Plasma levels of antioxidant vitamins, selenium, total sulfhydryl groups and oxidative products in ischemic-stroke patients as compared to matched controls in Taiwan. Free Radic Res 1998;28:15–24
5. Spencer AP, Carson DS, Crouch MA. Vitamin E and coronary artery disease. Arch Intern Med 1999;159: 1313–20
6. Ascherio A, Rimm EB, Hernan MA, et al. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. Ann Intern Med 1999;130:963–70
7. Gey KF, Stähelin HB, Eichholzer M. Poor plasma status of carotene and vitamin C is associated with higher mortality from ischemic heart disease and stroke: Basel Prospective Study. Clin Invest 1993; 71:3–6
8. Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary artery disease in a cohort of elderly people. BMJ 1995;310:1563–6
9. Keli SO, Hertog MG, Feskens EJ, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. Arch Intern Med 1996;156:637–42
10. Ross RK, Yuan JM, Henderson BE, et al. Prospective evaluation of dietary and other predictors of fatal stroke in Shanghai, China. Circulation 1997;96:50–5
11. Daviglus ML, Orencia AJ, Dyer AR, et al. Dietary vitamin C, beta-carotene and 30-year risk of stroke: results from the Western Electric Study. Neuroepidemiology 1997;16:69–77
12. Mark SD, Wang W, Fraumeni JF, et al. Do nutritional supplements lower the risk of stroke and hypertension? Epidemiology 1998;9:9–15
13. The Alpha-Tocopherol Beta-Carotene Cancer Pre-

vention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35
14. Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. JAMA 1974;230:1300–1
15. Anonymous. Megavitamin E supplementation and vitamin K–dependent carboxylation. Nutr Rev 1983;41:268–70
16. Polasek J. Acetylsalicylic acid and vitamin E in the prevention of arterial thrombosis. Can J Cardiol 1997;13:533–5
17. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996; 334:1145–9
18. Ascherio A, Rimm EB, Hernan MA, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 1998;98: 1198–204
19. Suter PM. The effect of potassium, magnesium, calcium, and fiber on risk of stroke. Nutr Rev 1999; 57:84–91
20. Tribble DL. Antioxidant consumption and risk of coronary heart disease: emphasis on vitamin C, vitamin E, and ß-carotene. Circulation 1999;99: 591–5
21. Deckelbaum RJ, Fisher EA, Winston M, et al. Summary of a scientific conference on preventive nutrition: pediatrics to geriatrics. Circulation 1999;100: 450–6
22. Segasothy M, Phillips PA. Vegetarian diet: panacea for modern lifestyle diseases? QJM 1999;92: 531–44
23. Potter JD, Steinmetz KS. Vegetables, fruit and phytoestrogens as preventive agents. IARC Sci Publ 1996;139:61–91
24. Williams GM, Williams CL, Weisburger JH. Diet and cancer prevention: the fiber first diet. Toxicol Sci 1999;52(2 suppl):72–86
25. Jansen MC, Bueno-de-Mesquita HB, Rasanen L, et al. Consumption of plant foods and stomach cancer mortality in the Seven Countries Study. Is grain consumption a risk factor? Seven Countries Study Research Group. Nutr Cancer 1999;34:49–55
26. Elkind MS, Sacco RL. Stroke risk factors and stroke prevention. Semin Neurol 1998;18:429–40
27. van-der-Worp HB, Bar PR, Kappelle LJ, de-Wildt DJ. Dietary vitamin E levels affect outcome of permanent focal cerebral ischemia in rats. Stroke 1998;29:1002–5
28. Wilson JX. Antioxidant defense of the brain: a role for astrocytes. Can J Physiol Pharmacol 1997;75: 1149–63
29. Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. Free Radic Biol Med 1997;22:359–78
30. Altura BM, Gebrewold A. Alpha-tocopherol attenuates alcohol-induced cerebral vascular damage in rats: possible role of oxidants in alcohol brain pathology and stroke. Neurosci Lett 1996;220:207–10
31. Tagami M, Ikeda K, Yamagata K, et al. Vitamin E prevents apoptosis in hippocampal neurons caused by cerebral ischemia and reperfusion in stroke-prone spontaneously hypertensive rats. Lab Invest 1999;79:609–15
32. Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. Int J Epidemiol 1997;26:1–13
33. Joshipura KJ, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. JAMA 1999;282:1233–9
34. Artalejo FR, Guallar-Castillon P, Banegas JR, et al. Consumption of fruit and wine and the decline in cerebrovascular disease mortality in Spain (1975–1993). Stroke 1998;29:1556–61
35. Blot WJ, Li JY, Taylor PR, et al. The Linxian trials: mortality rates by vitamin-mineral intervention group. Am J Clin Nutr 1995;62(suppl):1424S–6S
36. Kok FJ, DeBruijin AM, Vermeeren R, et al. Serum selenium, vitamin antioxidants and cardiovascular mortality: a 9-year follow-up study in the Netherlands. Am J Clin Nutr 1987;45:462–8
37. Klungel OH, Stricker BHC, Paes AHP, et al. Excess stroke among hypertensive men and women attributable to undertreatment of hypertension. Stroke 1999;30:1312–8